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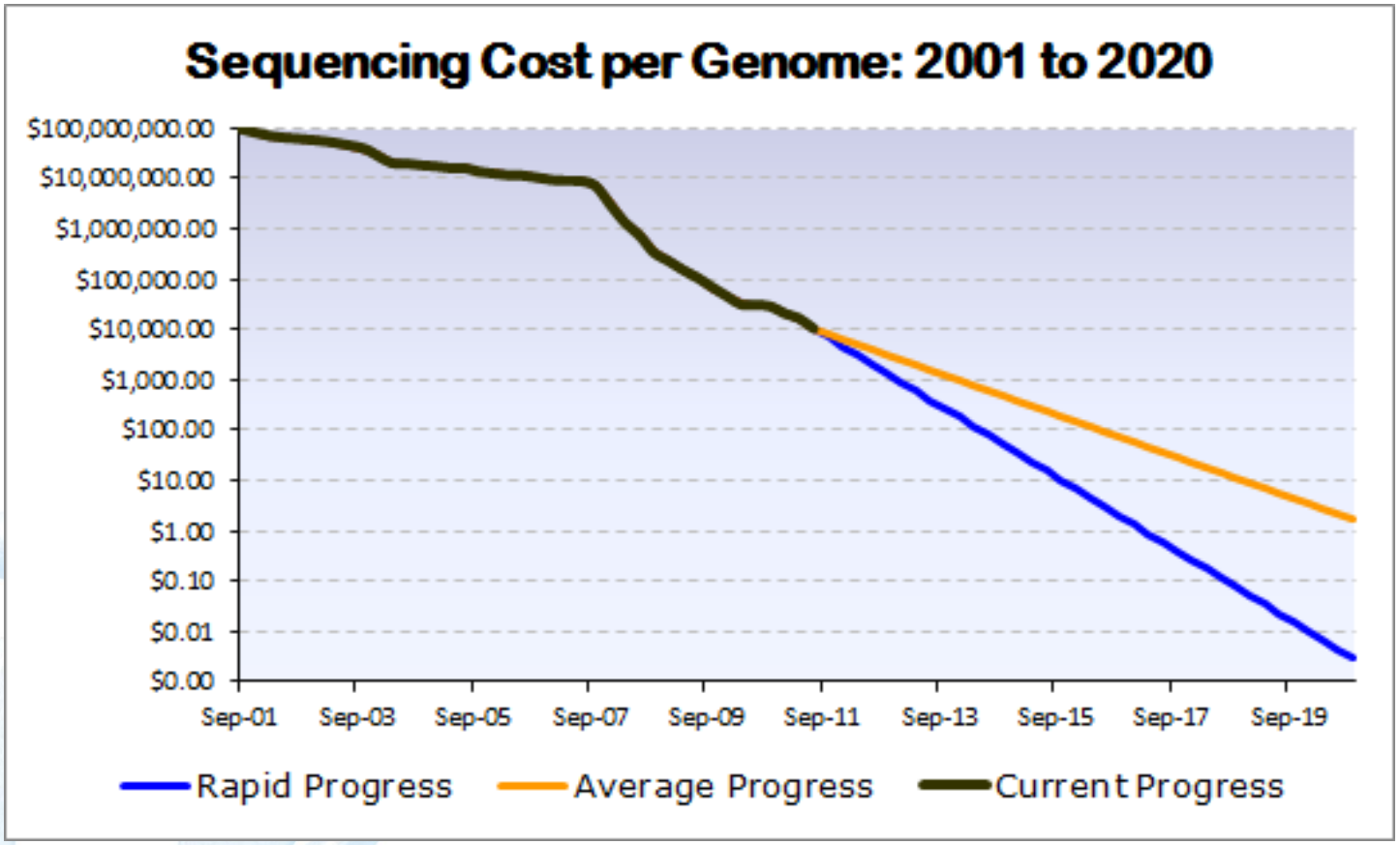
Ethische uitdagingen van *Next Generation Sequencing*

Pascal Borry
Centrum voor Biomedische Ethiek en Recht

Decreasing cost



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Diagnostics

Whole genome sequencing will further increase diagnostic yields

1. Consistent coverage. Coverage across the exome is highly variable: although WES is typically undertaken at high mean coverage (>100X), >20X coverage achieved over only ~85% of targeted coding regions [5]. WGS provides very consistent coverage - at 40X mean coverage, >96% of the mappable genome is covered at >20X depth.

Diagnostic yields for ID with WGS estimated >60%

LETTER

doi:10.1038/nature13394

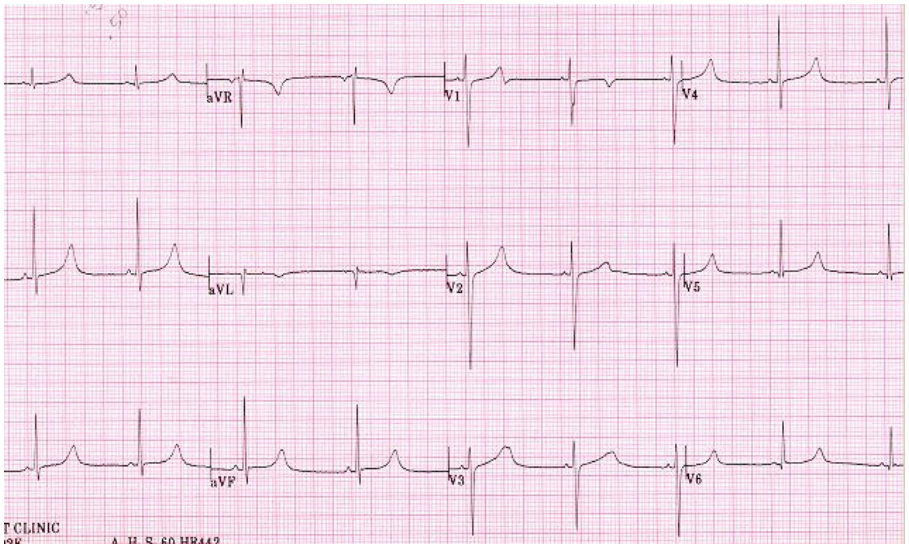
Genome sequencing identifies major causes of severe intellectual disability

Christian Gilissen[1]*, Jayne Y. Hehir-Kwa[1]*, Djie Tjwan Thung[1], Maartje van de Vorst[1], Bregje W. M. van Bon[1], Marjolein H. Willemsen[1], Michael Kwint[1], Irene M. Janssen[1], Alexander Hoischen[1], Annette Schenck[1], Richard Leach[2], Robert Klein[2], Rick Tearle[2], Tan Bo[1,3], Rolph Pfundt[1], Helger G. Yntema[1], Bert B. A. de Vries[1], Tjitske Kleefstra[1], Han G. Brunner[1,4]*, Lisenka E. L. M. Vissers[1]* & Joris A. Veltman[1,4]*

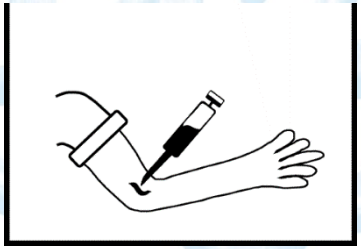
Nature, June 2014

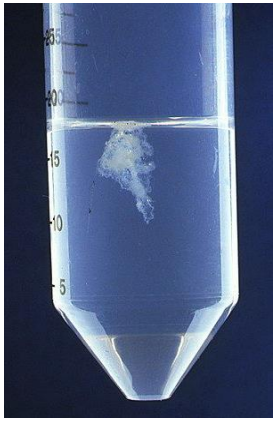
6. Diagnostic yield. Diagnostic yield from clinical whole genomes is significantly higher than exomes, due to their consistent coverage across exons, splice sites, and the detection of noncoding variants and CNVs.

Sudden cardiac arrest



Long QT syndrome ?





LQT1
LQT2
LQT3
LQT4
LQT5
LQT6
LQT7
LQT8
LQT9
LQT10
LQT11
LQT12
LQT13

ATTGTACGTGATGACCAGTGGAAT
ACCGTAAGGTAAAGTACCGTGTAC

Courtesy Koen Devriendt

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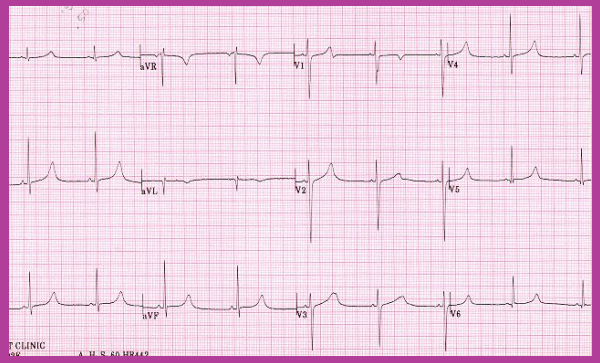
Expert- and analysis system



Clinical question
LQTS ?

LQTS?

ATTGTACGTGATGACCAGTGGAAT
ACCGTAAGGTAAAGTACCGTGTAC
TCGGTTGGAAGCTAGACTGAAGC
CAACCGTGGTAATCGTGTCCGTG
TACAAGGTTAGTAATGTACCATTGA
TCGGTAATACGTGGGCGTGGC
GTAACAGACTGACTGACCATCCTG
GTAGCTAGTCAAGTCGTAGCTGTC
GTCGACGAACGTATATGACACACG
TCAGTACGGTCAGTACACACATGC
TGTGGTGCAGTACAGATACAGTAC
AGATTAGCAGAAATGCAGATTTAGT

LQT1 LQT2 LQT3
LQT4 LQT5 LQT6
LQT7 LQT8 LQT9
LQT10 LQT11 LQT12
LQT13

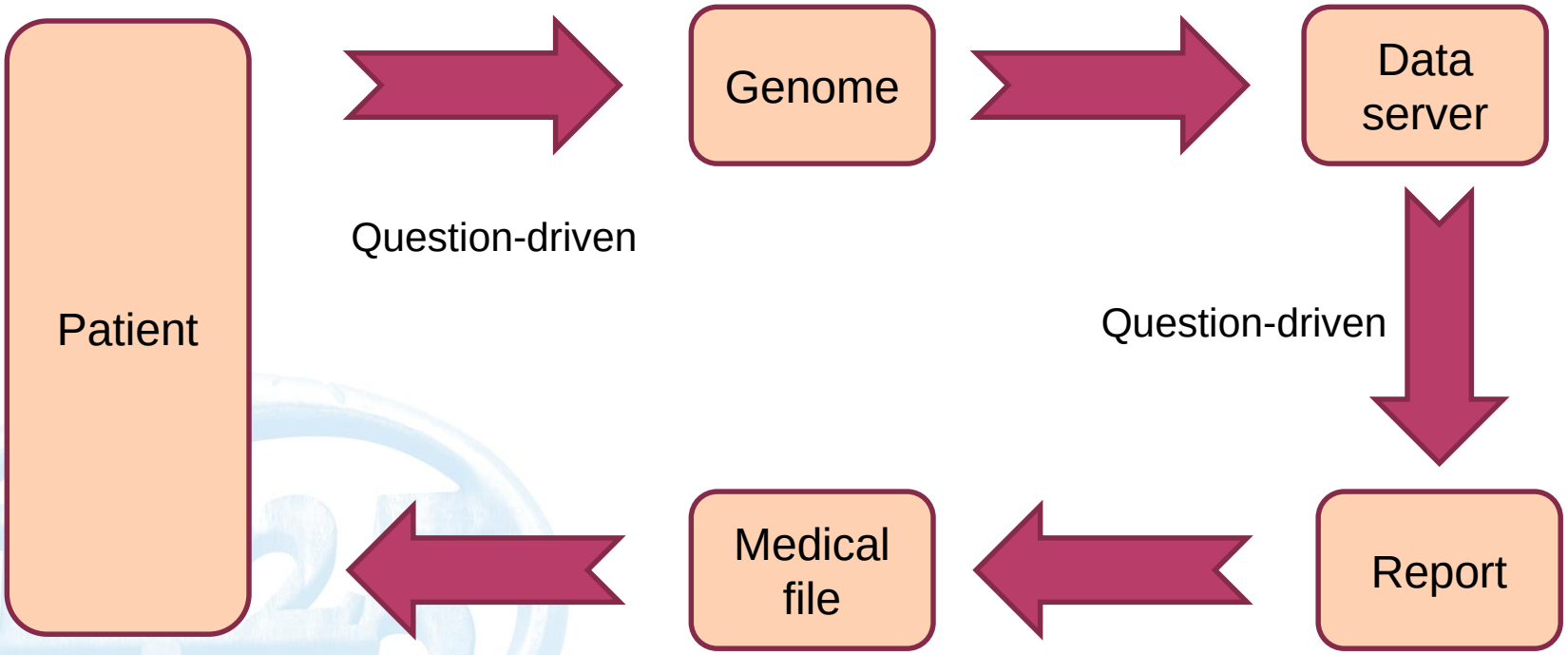
LQT15

Medical file

sequence data

Courtesy Koen Devriendt

Clinical NGS



Classified and unclassified variants

- Three different categories, i.e. pathogenic, benign and unclassified variants
- Focus on causal variants for a specific disorder (ESHG)
- If a causal variant cannot be detected then a wider analysis may be considered (ESHG)
- Communication of unclassified variants?
  - From lab to clinician?
  - From clinician to patient?

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Mutation databases

- Importance of locus-specific databases with information about the clinical interpretation of the databases
- Importance that all laboratories have a policy of submitting all variants to such databases

EJHG Open

European Journal of Human Genetics (2013) 21, 585–588

www.nature.com/ejhg

POLICY

The next controversy in genetic testing: clinical data as trade secrets?

Robert Cook-Deegan*[,1,2], John M Conley[3,4], James P Evans[5] and Daniel Vorhaus[4]

Is there a duty to follow up and to recontact?

- Duty of care?
- General consensus: “a general duty of recontact patients cannot be maintained” (ESHG)
  - Too burdensome
  - Not proportional
  - Patients who are discharged from care should know that they have the responsibility to recontact physicians for eventual follow-up
- Recontact in exceptional situations
- Communications through patient organisations, websites, forums, news...

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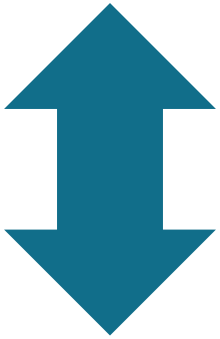
Incidental findings

Parallel to other incidental findings

- “This incorrectly assumes that analysis of clinically beneficial incidental findings is a **discrete test** requiring separate consent, whereas in reality it is **integral to the primary interrogation**.” (McGuire 2013)



- Needs additional operations and analysis (Burke 2013)
- **Risk of disease** versus **disease process** (PHG 2013)

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Terminology

- incidental findings,
- unsolicited variants,
- unanticipated results,
- secondary variants,
- unexpected or off-target results,
- unsought results, or unrelated findings
- non-incidental secondary findings,
- serendipitous or iatrogenic findings
- *“unsolicited finding to mean a result found during research or clinical testing that is beyond the aims of the study, or the original reason to conduct clinical testing.”*

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ESHG

- “it is preferable to use a targeted approach first in order to **avoid unsolicited findings or findings that cannot be interpreted.”**
- **Filtering**

Whole-genome sequencing in health care

Recommendations of the European Society of Human Genetics

Carla G van El[1], Martina C Cornel[1,2,3], Pascal Borry[4], Ros J Hastings[5], Florence Fellmann[6], Shirley V Hodgson[7], Heidi C Howard[8,9], Anne Cambon-Thomsen[8,9], Bartha M Knoppers[10], Hanne Meijers-Heijboer[11], Hans Scheffer[12], Lisbeth Tranebjaerg[13,14,15], Wybo Dondorp[16,17], Guido MWR de Wert[3,16,17]
on behalf of the ESHG Public and Professional Policy Committee

European Journal of Human Genetics (2013) **21**, 580–584; doi:10.1038/ejhg.2013.46

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ESHG

- “Guidelines for informed consent regarding diagnostic testing need to be developed. Patients’ claims to **a right not to know** do not automatically over-ride **professional responsibilities when the patient’s own health or that of his or her close relatives are at stake.** Patient groups could provide important input into how this should be handled.”

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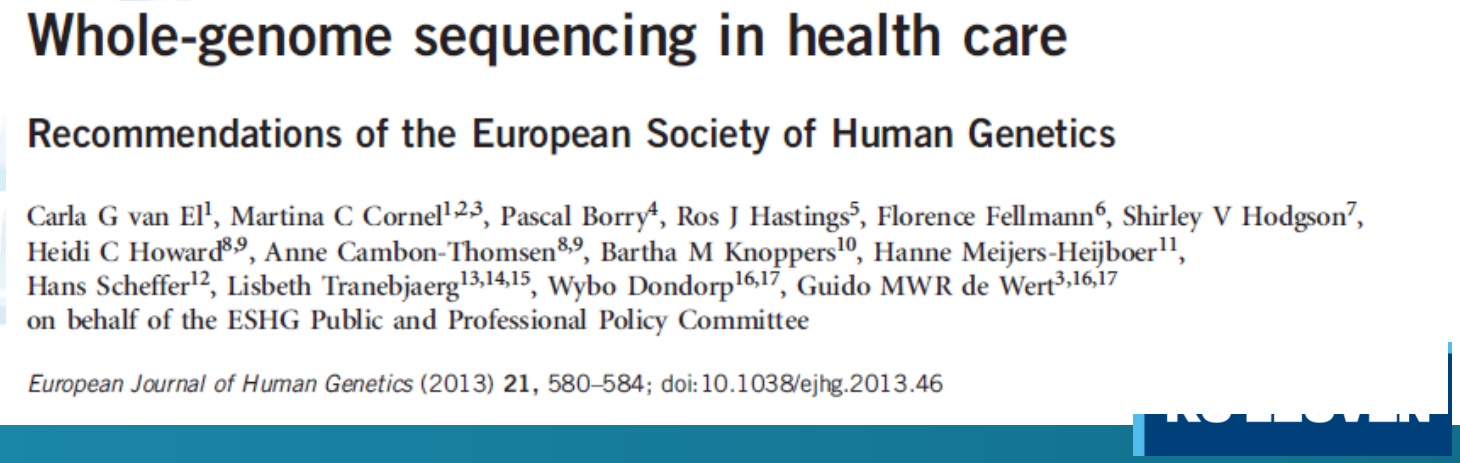
- “Whenever the use of these techniques is considered, a **protocol has to be in place to give guidance on the reporting of unsolicited findings**. If the detection of an unsolicited genetic variant is indicative of **serious health problems (either in the person tested or his or her close relatives) that allow for treatment or prevention**, in principle, a health-care professional should report such genetic variants.”



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Clinical NGS & secondary findings

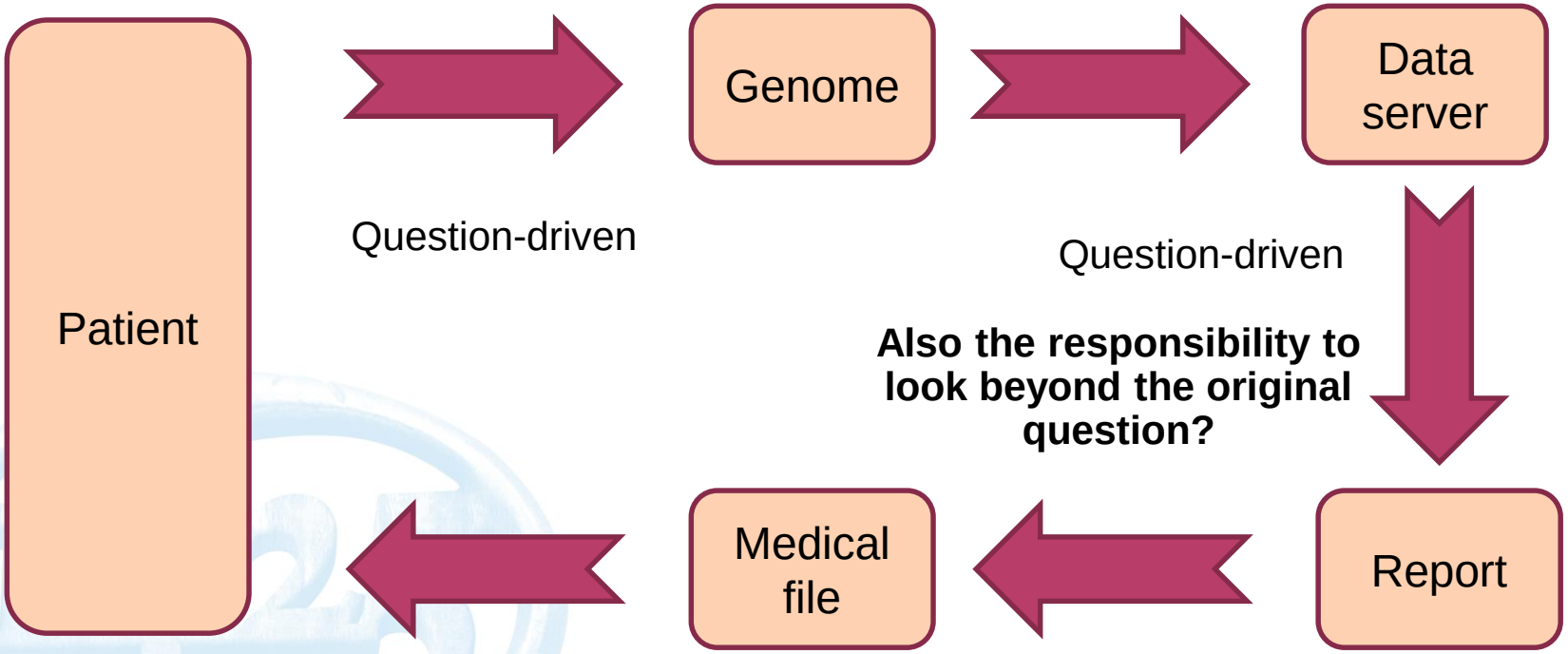

Table 1: Conditions, genes, and variants recommended for return of incidental findings in clinical sequencing

Phenotype	MIM-disorder	PMID-Gene Reviews entry	Typical age of onset	Gene	MIM-gene	Inheritance[a]	Variants to report[b]
Hereditary breast and ovarian cancer	604370 612555	20301425	Adult	*BRCA1* *BRCA2*	113705 600185	AD	KP and EP
Li–Fraumeni syndrome	151623	20301488	Child/adult	*TP53*	191170	AD	KP and EP
Peutz–Jeghers syndrome	175200	20301443	Child/adult	*STK11*	602216	AD	KP and EP
Lynch syndrome	120435	20301390	Adult	*MLH1* *MSH2* *MSH6* *PMS2*	120436 609309 600678 600259	AD	KP and EP
Familial adenomatous polyposis	175100	20301519	Child/adult	*APC*	611731	AD	KP and EP
MYH-associated polyposis; adenomas, multiple colorectal, *FAP* type 2; colorectal adenomatous polyposis, autosomal recessive, with pilomatricomas	608456 132600	23035301	Adult	*MUTYH*	604933	AR[c]	KP and EP
Von Hippel–Lindau syndrome	193300	20301636	Child/adult	*VHL*	608537	AD	KP and EP
Multiple endocrine neoplasia type 1	131100	20301710	Child/adult	*MEN1*	613733	AD	KP and EP
Multiple endocrine neoplasia type 2	171400 162300	20301434	Child/adult	*RET*	164761	AD	KP
Familial medullary thyroid cancer[d]	1552401	20301434	Child/adult	*RET*	164761	AD	KP
PTEN hamartoma tumor syndrome	153480	20301661	Child/adult	*PTEN*	601728	AD	KP and EP
Retinoblastoma	180200	20301625	Child	*RB1*	614041	AD	KP and EP
Hereditary paraganglioma–pheochromocytoma syndrome	168000 (PGL1) 601650 (PGL2) 605373 (PGL3) 115310 (PGL4)	20301715	Child/adult	*SDHD* *SDHAF2* *SDHC* *SDHB*	602690 613019 602413 185470	AD	KP and EP KP KP and EP
Tuberous sclerosis complex	191100 613254	20301399	Child	*TSC1* *TSC2*	605284 191092	AD	KP and EP
WT1-related Wilms tumor	194070	20301471	Child	*WT1*	607102	AD	KP and EP
Neurofibromatosis type 2	101100	20301380	Child/adult	*NF2*	607379	AD	KP and EP
Ehlers–Danlos syndrome, vascular type	130050	20301667	Child/adult	*COL3A1*	120180	AD	KP and EP
Marfan syndrome, Loeys–Dietz syndromes, and familial thoracic aortic aneurysms and dissections	154700 609192 608967 610168 610380 613795 611788	20301510 20301312 20301240	Child/adult	*FBN1* *TGFBR1* *TGFBR2* *SMAD3* *ACTA2* *MYLK* *MYH11*	134797 190181 190182 603109 102620 600922 160745	AD	KP and EP
Hypertrophic cardiomyopathy, dilated cardiomyopathy	115197 613690 613642 613116 601494 612098 600858 301500 608758 115200	20301724	Child/adult	*MYBPC3* *MYH7* *TNNT2* *TNNI3* *TPM1* *MYL3* *ACTC1* *PRKAG2* *GLA* *MYL2* *LAMP2*	600958 160760 191045 191044 191010 160790 102540 602743 300644 160781 150330	AD XL AD 	KP and EP KP KP and EP KP KP and EP (hemi, het, hom) KP KP and EP
Catecholaminergic polymorphic ventricular tachycardia	604772			*RYR2*	180902	AD	KP
Arrhythmogenic right-ventricular cardiomyopathy	609040 604400 610476 611528 610450	20301310	Child/adult	*PKP2* *DSP* *DSC2* *TMEM43* *DSG2*	602861 125647 125645 612048 125671	AD	KP and EP KP KP and EP
Romano–Ward long QT syndrome types 1, 2, and 3, Brugada syndrome	192500 613688 603830 601144	20301472	Child/adult	*KCNQ1* *KCNH2* *SCN5A*	607542 152427 600163	AD	KP and EP
Familial hypercholesterolemia	143890 603776	No GeneReviews entry	Child/adult	*LDLR* *APOB* *PCSK9*	606945 107730 607786	SD SD AD	KP and EP KP
Malignant hyperthermia susceptibility	145600	20301325	Child/adult	*RYR1* *CACNA1S*	180901 114208	AD	KP

[a]Some conditions that may demonstrate semidominant inheritance (SD) have been indicated as autosomal dominant (AD) for the sake of simplicity. Others have been labeled as X-linked (XL); [b]KP: known pathogenic, sequence variation is previously reported and is a recognized cause of the disorder; EP: expected pathogenic, sequence variation is previously unreported and is of the type that is expected to cause the disorder. Note: The recommendation to not report expected pathogenic variants for some genes is due to the recognition that truncating variants, the primary type of expected pathogenic variants, are not an established cause of some diseases on the list. [c]Although carriers may have modestly increased risk, we recommend searching only for individuals with biallelic mutations; [d]On the basis of evidence presented to the Working Group after the online posting of these Recommendations, the decision was made to remove one gene, NTRK1, from the recommended list.

Tables index

ACMG recommendation

"Minimum list of incidental findings to report from clinical sequencing"

Is this screening?

- “In reality, seeking and reporting of incidental findings represents a form of ‘**opportunistic screening**’” (ACMG guideline)

ACMG recommendations

- The ACMG argues that laboratories have **a fiduciary duty** to seek and return such results for the **57 genes** on its list to all patients, regardless of **patient preferences** or **age**.
- “disorders where **preventative measures and/or treatments** were available and disorders in which individuals with pathogenic mutations might be asymptomatic for long periods of time”
- **Variants “that meet criteria for reporting as pathogenic”** (i.e. recognized cause of disorder; or expected to cause the disorder)
- “**actively search** for the specified types of mutations in the specified genes listed in these recommendations”
- **No opt out**

Statement 1. Professional obligation

- “The recommendations essentially argue that laboratory personnel have a **professional obligation** to conduct a comprehensive evaluation of available test results to identify such clinically significant findings.” (McGuire 2013)

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Critique 1: Professional obligation?

- ‘serious’ threat?
- ‘urgency of the need to disclose’?
- Childhood-onset conditions > adult-onset conditions?
- Certainty or Risk

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Statement 2: Clinical utility of “hunting”

- include only “unequivocally pathogenic mutations in genes where pathogenic variants lead to disease with **very high probability and where evidence strongly supports the benefits of early intervention**.” (McGuire et al. 2013)

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Critique 2: Clinical utility of “hunting”

- “**insufficient evidence** about benefits, risks and costs of disclosing incendental findings to make evidence-based recommendations” (ACMG guideline)
- Meaning in **low risk group** of pathogenic mutations?
- “The treshhold for determining which results should be returned to individuals seeking screening should be set significantly higher than that set for diagnostic testing due to the **much lower a priori chance of disease** in such individuals.” (ACMG 2012)

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Statement 3: Patient preferences

- Patient **can't opt out** as to whether or not to receive the minimum list of incidental findings
- "**patients have the right to decline clinical sequencing** if they judge the risks of possible discovery of incidental findings to outweigh the benefits of testing." (ACMG guideline)

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Critique 3: Patient preferences?

- “Patients should be given the option of not receiving...secondary findings.” (ACMG 2012)
- Violation of patient autonomy with regard to return of results (there is no opt out)
- Patients might refuse testing overall
- Concern of liability
- Patient experiences and interests

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ACMG
American College of Medical Genetics and Genomics
Translating Genes Into Health®

ACMG NEWS

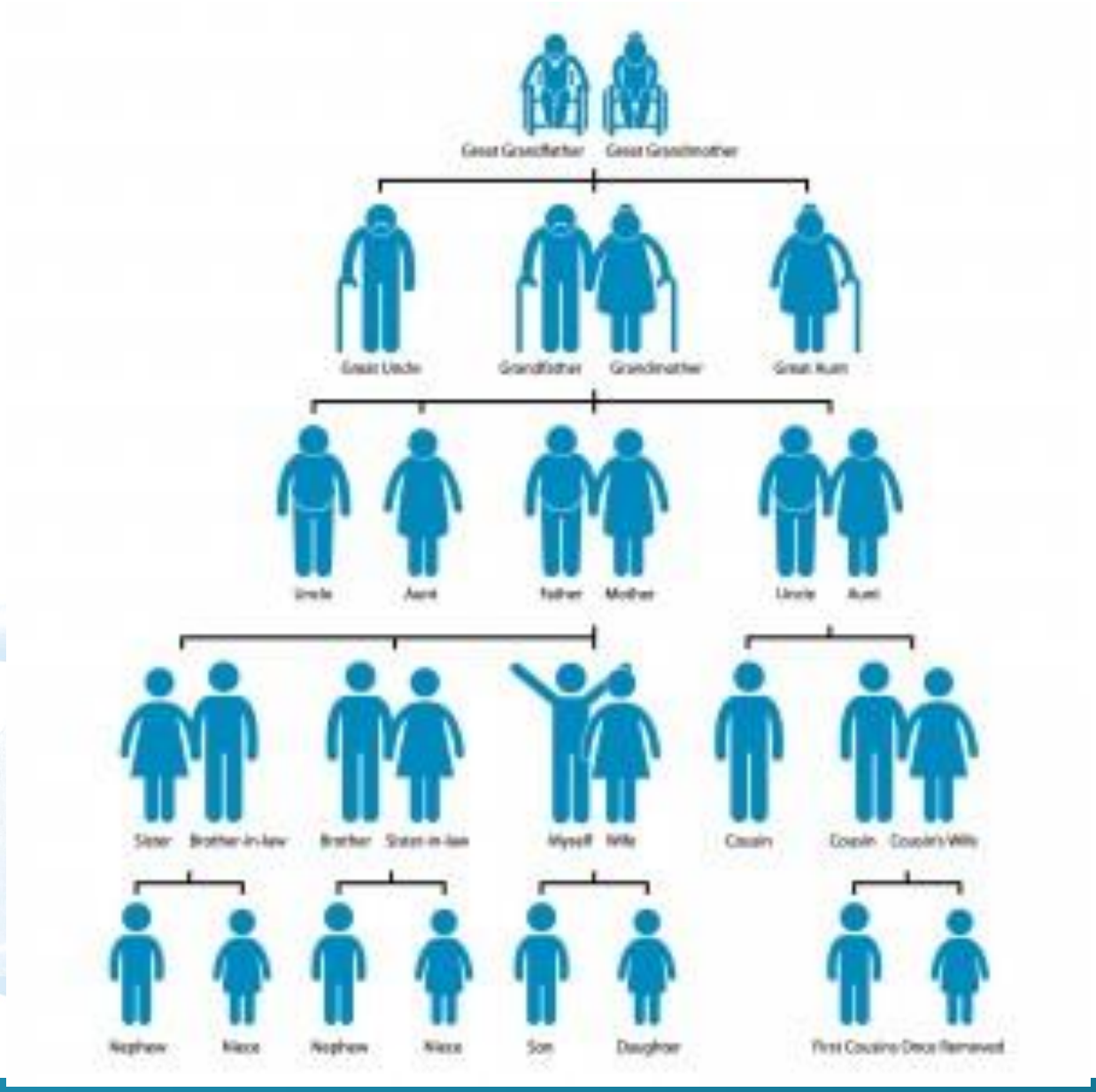
Media Contact: ACMG Media Relations
kbeal@acmg.net

ACMG Updates Recommendation on "Opt Out" for Genome Sequencing Return of Results

Bethesda, MD - April 1, 2014| There has been significant discussion surrounding the initial ACMG recommendations for the return of results from genome-scale sequencing issued in March of 2013. The ACMG Board of Directors has listened carefully to the members' views and appreciates the many forums in which divergent and valuable opinions have been expressed. The positions of ACMG members regarding the issues raised by the recommendations have been assessed through a variety of mechanisms, including direct feedback, participation by Board members in numerous forums exploring these issues, informal conversations, published articles, commentaries and, most recently, through an extensive member survey, the results of which were presented at the ACMG Annual Business meeting at the 2014 ACMG Annual Clinical Genetics Meeting in Nashville on Thursday, March 27.

There appears to be a consensus among ACMG members that patients should have an opportunity to opt out of the analysis of medically actionable genes when undergoing whole exome or genome sequencing. While the ACMG Board still considers the IFs to be important medical information that can be a great value to families, it has voted to recommend that such an "opt out" option be offered to patients who are considered candidates for clinical genome-scale sequencing. "This update to our recommendations moves the opt out discussion to the point where the sample is sent rather than at the time when results are received by the ordering clinician, as was originally recommended," explained Gail Herman, MD, PhD, FACMG, president of the American College of Medical Genetics and Genomics. Explanation to patients of the opt-out option and its implications should be part of the general education and informed consent process undertaken by the ordering clinician prior to ordering the test.

LEUVEN


Great Grandfather
Great Grandmother
Great Uncle
Grandfather
Grandmother
Great Aunt
Uncle
Aunt
Father
Mother
Uncle
Aunt
Sister
Brother-in-law
Brother
Sister-in-law
Myself
Wife
Cousin
Cousin
Cousin's Wife
Nephew
Niece
Nephew
Niece
Son
Daughter
First Cousins Once Removed

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Redenen waarom informatie niet wordt doorgegeven

- Geen nauwe relatie
- Verlangen om familieleden te beschermen tegen ‘slecht nieuws’
- Perceptie van laag risico (ongetrouwd, kinderloos, geen plannen voor kinderen…)
- Familievetes
- Betrokkene is te jong
- Veronderstelling dat anderen de informatie reeds hebben gegeven
- Negatieve houding ten opzichte van zwangerschapsafbreking
- Taboe
- Schuldgevoelens
- Angst (bvb. Boodschapper van slecht nieuws)
- Vrees voor negatieve impact (bvb. op huwelijk)

Redenen waarom informatie wel wordt doorgegeven:

- Morele verplichting
- Reproductieve risico’s
- Nauwe banden
- Verantwoordelijkheid tegenover jongere generaties
- In sommige gevallen medisch voordeel

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Beroepsgeheim

Doorschuiven van verantwoordelijkheid naar familieleden

- ‘familiebrieven’

- Gegronde reden om beroepsgeheim te doorbreken?

1) Alles is geprobeerd om toestemming van de patiënt te krijgen?

2) Ernstige schade voor een ander bij handhaving geheim

3) Arts verkeert in gewetensnood door handhaving van het geheim

4) Er is geen andere weg om het probleem op te lossen dan het doorbreken van het geheim

5) Schade aan de ander kan vrijwel zeker voorkomen worden of beperkt door het doorbreken van het geheim

6) Het geheim wordt zo min mogelijk geschonden?

Beroepsgeheim doorbreken

- Australië:

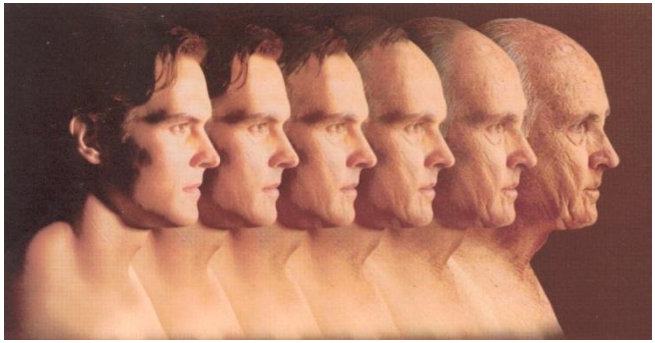
  “**to permit** a health professional to disclose genetic information about his or her patient to genetic relative of that patient where the disclosure is necessary to lessen or prevent a serious threat to an individual’s life, health or safety, even where the threat is not imminent.”

Beroepsgeheim doorbreken

- Australië: voorwaarden

1) Voorafgaand informeren van de patiënt dat informatie relevant kan zijn voor de familieleden van de patiënt en dat zorgverleners deze kunnen meedelen
2) Redelijke stappen om patiënt te overtuigen
3) Niet om het even welke arts kan deze familieleden contacteren
4) Overleg met collega's over doorbreken van beroepsgeheim
5) Informatie beperken tot strikt noodzakelijke en identificatie van patiënt vermijden, net als het feit dat deze de informatie weigerde te geven
6) Beperking tot derdegraadsverwanten

Genomics during the lifecycle



Neonatal Preconceptional Prenatal During life

SCREENING

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Hoge Gezondheidsraad
Conseil Supérieur de la Santé

Carrier screening in a reproductive context: Towards a responsible implementation in the healthcare system

- *P Borry, M Van den Bulcke,*
- *H Van Oyen for the workgroup Public Health Genomics*

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DOMINANT GEN
iedereen
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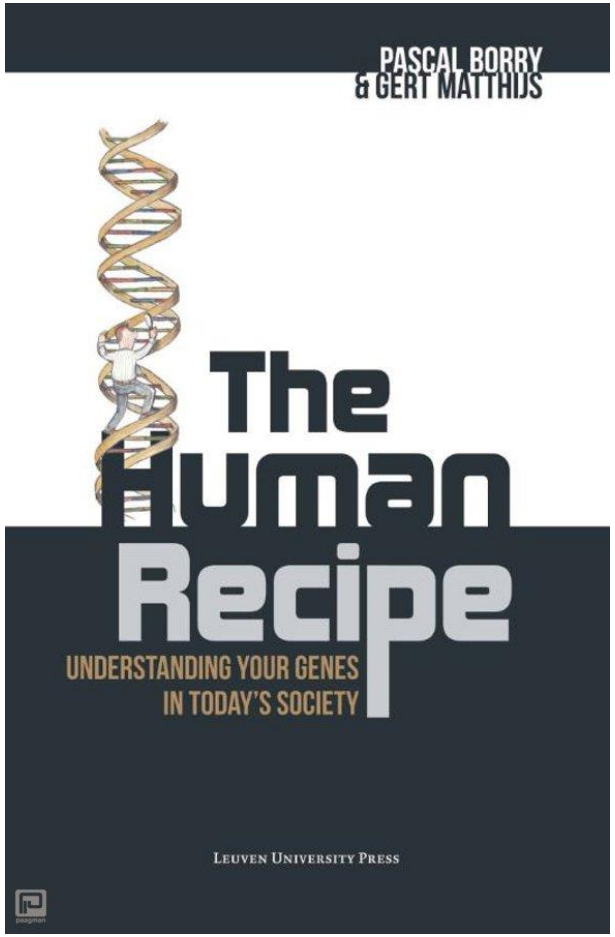
HUMANE GENETICA IN WOORDEN & CARTOONS
Pascal Borry
Gert Matthijs
Bilcan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